Responses to reviewers

Reviewer #1:
Specific Comments to Authors:
Here, I have some concerns about this review:

1. As title "Clinical relevance of stem cells in lung cancer", the authors should add more information about "clinical", such as drugs (target lung cancer stem cells) and clinical trials(about lung cancer stem cells).

We agree and appreciate the reviewer's suggestions. A section entitled "STEM CELL MARKERS AS THERAPEUTIC TARGETS FOR THE TREATMENT OF LUNG CANCER" is added to the manuscript. The section describes the clinical trials and preclinical studies developed in murine models. In particular, those using new therapeutic agents directed against molecular biomarkers that are expressed in lung cancer stem cells. A table summarizing the therapeutic strategies targeting lung cancer stem cell biomarkers has been added to the manuscript.

2. These reference should be updated.

Updated references to pertinentsections have been added to the manuscript.

3. Any unique character(s) of lung cancer stem cells, compared with other malignant cancers?

Under physiological conditions, normal stem cells are found in a low proportion in almost all tissues. In fact, their phenotypic and functional properties are independent from the tissue of origin. Normal stem cells play an essential role in tissue repair, although their cell division is finely controlled.
Lung cancer stem cells could originate from tissue-specific normal stem cells through deregulation of signaling pathways such as Notch, Hedgehog and Wnt pathways, leading to uncontrolled growth.
Biomarkers expressed cancer stem cells are not specific for any type of tumor. Moreover, biomarkers for lung cancer stem cells are expressed in other types of cancer, such as breast, brain, colon, or liver.

Reviewer #2:
Specific Comments to Authors:

1. Please summarize the "Cluster of differentiation" section, preferably making a table.

A summary of the stem cell biomarkers in lung cancer is now described in figure 2 (page 27 of the manuscript).

2. In "CONCLUSIONS AND FUTURE PERSPECTIVES" section, please summarize the Clinical trials with CSCs, preferably list them.

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